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(FILE 'HOME' ENTERED AT 12:28:02 ON 17 JAN 2006)

FILE 'MEDLINE, CAPLUS, BIOSIS' ENTERED AT 12:28:32 ON 17 JAN 2006

L1 33098 S LEPTIN
L2 83497 S ANGIOGENESIS
L3 570 S ANG2
L4 270 S L1 (L) L2
L5 183 S L2 (L) L3
L6 86 DUP REM L5 (97 DUPLICATES REMOVED)
L7 37 S L6 AND PY<2003
L8 496701 S ENDOTHEL?
L9 33 S L7 (L) L8
L10 10 S L9 AND INHIBITOR
E RUBINSTEIN MENCACHEM /AU
L11 246 S E1
E COHEN BATYA /AU
L12 41 S E3 OR E2
E BARKAN DALIT /AU
L13 15 S E3
L14 271 S L11 OR L12 OR L13
L15 1 S L14 AND LEPTIN AND ANGIOGENESIS

L15 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN

TI **Leptin** for use in inhibition of endothelial cell proliferation optionally together with VEGF inhibitors

IN **Rubinstein, Menachem; Cohen, Batya; Barkan, Dalit**

AB Disclosed is the use of **leptin**, optionally together with VEGF inhibitors, in inhibition of endothelial cell proliferation and modulation of **angiogenesis**, for use in the female reproductive tract or for use in adipose tissue regression. Pharmaceutical compns. are also claimed.

ST **leptin** VEGF antagonist compn endothelium proliferation **angiogenesis** inhibition

IT Blood vessel
(endothelium; **leptin** for use in inhibition of endothelial cell proliferation optionally together with VEGF inhibitors)

IT Reproductive tract
(female; **leptin** for use in inhibition of endothelial cell proliferation in female reproductive tract optionally together with VEGF inhibitors)

IT Vascular endothelial growth factor receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene flt 1; pharmaceutical compns. for inhibiting endothelial cell proliferation comprising **leptin** or **leptin** analog or derivative optionally with inhibitor of VEGF action or synthesis and/or inhibitor of **angiogenesis**)

IT **Angiogenesis** inhibitors
(**leptin** for use in inhibition of endothelial cell proliferation and for modulation of **angiogenesis** optionally together with VEGF inhibitors)

IT Antiobesity agents
(**leptin** for use in inhibition of endothelial cell proliferation and for regression of adipose tissue optionally together with VEGF inhibitors)

IT Proliferation inhibition
(**leptin** for use in inhibition of endothelial cell proliferation optionally together with VEGF inhibitors)

IT Drug delivery systems
(pharmaceutical compns. for inhibiting endothelial cell proliferation comprising **leptin** or **leptin** analog or derivative optionally with inhibitor of VEGF action or synthesis and/or inhibitor of **angiogenesis**)

IT 194368-66-6, Angiopoietin 2
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(**leptin** for use in inducement of angiopoietin 2 optionally together with VEGF inhibitors)

IT 83-67-0, Theobromine 145-63-1, Suramin 519-37-9, 7-(β -Hydroxyethyl)theophylline 961-45-5, 8-Phenyltheophylline 14114-46-6, DMPX 37270-94-3, Platelet factor-4 53902-12-8, Tranilast 147700-11-6, 8-(3-Chlorostyryl)caffeine 169494-85-3, **Leptin** 169494-85-3D, **Leptin**, homologs and derivs. 200725-10-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**leptin** for use in inhibition of endothelial cell proliferation optionally together with VEGF inhibitors)

IT 127464-60-2, Vascular endothelial growth factor
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(**leptin** for use in inhibition of endothelial cell proliferation optionally together with VEGF inhibitors)

L15 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
TI **Leptin** for use in inhibition of endothelial cell proliferation
optionally together with VEGF inhibitors
IN **Rubinstein, Menachem; Cohen, Batya; Barkan,
Dalit**
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
PY 2001
2001
2001
2001
2005
2002
2002
2003
2003
2003
2002
2005

=> d l10 1-10 ti au py so kwic

L10 ANSWER 1 OF 10 MEDLINE on STN
TI A computer algorithm describing the process of vessel formation and maturation, and its use for predicting the effects of anti-angiogenic and anti-maturation therapy on vascular tumor growth.
AU Arakelyan L; Vainstein V; Agur Z
PY 2002
SO Angiogenesis, (2002) 5 (3) 203-14.
Journal code: 9814575. ISSN: 0969-6970.
SO Angiogenesis, (2002) 5 (3) 203-14.
Journal code: 9814575. ISSN: 0969-6970.
AB . . . forward an algorithm describing the three principal interconnected sub-processes that influence tumor and vasculature dynamics: (i) tumor cell proliferation (ii) **angiogenesis**, that is, the formation and regression of immature vessels (IV), and (iii) maturation, i.e., the formation and destabilization of mature. . . and organ levels. Implementing this complex algorithm in a computer model, one can evaluate the correlations between various factors influencing **angiogenesis** and their influence on tumor progression at any given moment. Moreover, the computer simulations enable analysis of the versatile effects. . . blood vessels, as well as on the induction of an array of relevant growth factors such as angiopoietin-1 (Ang1), angiopoietin-2 (**Ang2**), vascular **endothelial** growth factor (VEGF) and platelet-derived growth factor (PDGF). Simulation results suggest that vessel maturation and destabilization of MV drive the. . .
CT *Algorithms
 ***Angiogenesis Inhibitors: TU, therapeutic use**
 Disease Progression
 Endothelial Growth Factors: GE, genetics
 Humans
 Intercellular Signaling Peptides and Proteins: GE, genetics
 Lymphokines: GE, genetics
 Models, Biological
 *Neoplasms: BS, blood supply
 Neoplasms: DT, drug therapy
 *Neoplasms: PA, pathology
 *Neovascularization, Pathologic
 Research Support, Non-U.S. Gov't
 Vascular Endothelial Growth Factor A
 Vascular Endothelial Growth Factors
CN 0 (**Angiogenesis Inhibitors**); 0 (**Endothelial Growth Factors**); 0 (Intercellular Signaling Peptides and Proteins); 0 (Lymphokines); 0 (Vascular **Endothelial Growth Factor A**); 0 (Vascular **Endothelial Growth Factors**)

L10 ANSWER 2 OF 10 MEDLINE on STN
TI Dual role of **Ang2** in postnatal **angiogenesis** and lymphangiogenesis.
AU Veikkola Tanja; Alitalo Kari
PY 2002
SO Developmental cell, (2002 Sep) 3 (3) 302-4.
Journal code: 101120028. ISSN: 1534-5807.
TI Dual role of **Ang2** in postnatal **angiogenesis** and lymphangiogenesis.
SO Developmental cell, (2002 Sep) 3 (3) 302-4.
Journal code: 101120028. ISSN: 1534-5807.
AB . . . the opposing processes of vessel growth and regression. A new study in this issue of Developmental Cell shows that Angiopoietin-2 (**Ang2**), a ligand for the **endothelial** Tie2 receptor tyrosine kinase, has a dual function in the processes of postnatal **angiogenesis** and vascular remodeling. Also, **Ang2** signals are required for the proper development and function of the lymphatic vessels.
CT *Angiogenesis Inducing Agents: PH, physiology
 Angiopoietin-2

Animals

*Blood Vessels: GD, growth & development

Blood Vessels: ME, metabolism

Embryo: ME, metabolism

Endothelial Growth Factors: GE, genetics

Endothelial Growth Factors: ME, metabolism

Endothelium, Vascular: CY, cytology

Endothelium, Vascular: ME, metabolism

*Lymphatic System: GD, growth & development

Lymphatic System: ME, metabolism

Mice

Mice, Knockout

Models, Biological

*Neovascularization, Physiologic

Platelet-Derived Growth Factor: ME, metabolism

Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors

Receptor Protein-Tyrosine Kinases: ME, metabolism

Signal Transduction

CN 0 (Angiogenesis Inducing Agents); 0 (Angiopoietin-2); 0 (Endothelial Growth Factors); 0 (Platelet-Derived Growth Factor); EC 2.7.1.112 (Receptor Protein-Tyrosine Kinases)

L10 ANSWER 3 OF 10 MEDLINE on STN

TI Angiopoietin-2 displays VEGF-dependent modulation of capillary structure and **endothelial** cell survival in vivo.

AU Lobov Ivan B; Brooks Peter C; Lang Richard A

PY 2002

SO Proceedings of the National Academy of Sciences of the United States of America, (2002 Aug 20) 99 (17) 11205-10. Electronic Publication: 2002-08-05.

Journal code: 7505876. ISSN: 0027-8424.

TI Angiopoietin-2 displays VEGF-dependent modulation of capillary structure and **endothelial** cell survival in vivo.

SO Proceedings of the National Academy of Sciences of the United States of America, (2002 Aug 20) 99 (17) 11205-10. Electronic Publication: 2002-08-05.

Journal code: 7505876. ISSN: 0027-8424.

AB Modulation of Tie2 receptor activity by its angiopoietin ligands is crucial for **angiogenesis**, blood vessel maturation, and vascular **endothelium** integrity. It has been proposed that angiopoietins 1 (Ang1) and 2 (**Ang2**) are pro- and anti-angiogenic owing to their respective agonist and antagonist signaling action through the Tie2 receptor. The function of **Ang2** has remained controversial, however, with recent reports suggesting that in some circumstances, it may be pro-angiogenic. We have examined this. . . vivo model for studying the effects of vascular regulators. We show that in vivo, in the presence of endogenous vascular **endothelial** growth factor (VEGF)-A, **Ang2** promotes a rapid increase in capillary diameter, remodeling of the basal lamina, proliferation and migration of **endothelial** cells, and stimulates sprouting of new blood vessels. By contrast, **Ang2** promotes **endothelial** cell death and vessel regression if the activity of endogenous VEGF is inhibited. These observations support a model for regulation of vascularity where VEGF can convert the consequence of **Ang2** stimulation from anti- to pro-angiogenic.

CT . . . Apoptosis: DE, drug effects

*Capillaries: CY, cytology

Capillaries: DE, drug effects

Cell Division: DE, drug effects

*Cornea: BS, blood supply

*Endothelial Growth Factors: PD, pharmacology

*Endothelium, Vascular: CY, cytology

Endothelium, Vascular: DE, drug effects

Enzyme Inhibitors: PD, pharmacology

Humans

*Lymphokines: PD, pharmacology

*Muscle, Smooth, Vascular: CY, cytology

Muscle, Smooth, Vascular: DE, drug effects

Proteins:. . . pharmacology

*Proteins: PH, physiology

Rats

Rats, Sprague-Dawley

Recombinant Proteins: PD, pharmacology

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.

Vascular Endothelial Growth Factor A

Vascular Endothelial Growth Factors

CN 0 (Angiopoietin-2); 0 (**Endothelial** Growth Factors); 0 (Enzyme
Inhibitors); 0 (Lymphokines); 0 (Proteins); 0 (Recombinant
Proteins); 0 (Vascular **Endothelial** Growth Factor A); 0 (Vascular
Endothelial Growth Factors)

L10 ANSWER 4 OF 10 MEDLINE on STN

TI Expression of angiopoietin-1, angiopoietin-2, and Tie2 genes in normal
ovary with corpus luteum and in ovarian cancer.

AU Hata Kohkichi; Udagawa Jun; Fujiwaki Ritsuto; Nakayama Kentaro; Otani
Hiroki; Miyazaki Kohji

PY **2002**

SO Oncology, (2002) 62 (4) 340-8.

Journal code: 0135054. ISSN: 0030-2414.

SO Oncology, (2002) 62 (4) 340-8.

Journal code: 0135054. ISSN: 0030-2414.

AB OBJECTIVE: The recent discovery of angiopoietin-1 (Ang1) and
angiopoietin-2 (**Ang2**) has provided novel and important insights
into the molecular mechanisms of blood vessel formation. Ang1 and
Ang2 bind with similar affinity to the **endothelial** cell
tyrosine kinase receptor Tie2. Our purpose was to assess the potential
role of the Ang/Tie2 system in physiological and pathological
angiogenesis in the ovary. METHODS: Ang1, **Ang2**, and
Tie2 gene expression in 14 normal ovaries with corpus luteum (CL) and in
19 cases of ovarian cancer were. . . was presented by the relative
yield of each gene to the beta(2)-microglobulin gene, respectively.
Furthermore, cellular distribution of Ang1 and **Ang2** mRNA was
examined by in situ hybridization, and localization of Tie2 was studied by
immunohistochemistry. RESULTS: The Ang1, **Ang2**, and Tie2 gene
expression in normal ovary with CL ranged from 0.18 to 1.06 (median 0.54),
0.31-2.64 (median 1.01), and. . . normal ovary with CL was
significantly higher than that in ovarian cancer ($p = 0.0004$). The gene
expression levels of **Ang2** and Tie2 were statistically the same
in both groups. There was a significant correlation between Ang1 gene
expression and Tie2. . . normal ovary with CL ($r = 0.619$, $p = 0.018$).
No such significant correlation was found in ovarian cancer. Moreover,
Ang2 gene expression showed no significant correlation with the
Tie2 gene expression either in normal ovary with CL or in ovarian cancer.
Transcripts for Ang1 were observed in CL cells and **endothelial**
cells around CL, and in tumor cells and **endothelial** cells at the
periphery of tumor invasion. **Ang2** transcripts were expressed in
the same patterns. Tie2 expression was positive primarily in the
endothelial cells around CL and in those at the periphery of tumor
invasion. CONCLUSION: Our results indicate that there is a difference in
the Ang/Tie2 gene expression between physiological and pathological
angiogenesis in the ovary. This finding may aid in the
development of new therapeutic interventions for ovarian cancer.
Copyright 2002 S. Karger. . .

CT . . .

Neoplasms: GE, genetics

Ovarian Neoplasms: ME, metabolism

*Ovary: ME, metabolism

*Proteins: GE, genetics

Proteins: ME, metabolism

RNA, Messenger: ME, metabolism

Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors

*Receptor Protein-Tyrosine Kinases: GE, genetics

Receptor Protein-Tyrosine Kinases: ME, metabolism

Receptor, TIE-2

Reverse. . .

L10 ANSWER 5 OF 10 MEDLINE on STN
 TI Expression of angiopoietin-1 in human glioblastomas regulates tumor-induced angiogenesis: in vivo and in vitro studies.
 AU Audero E; Cascone I; Zanon I; Previtali S C; Piva R; Schiffer D; Bussolino F
 PY 2001
 SO Arteriosclerosis, thrombosis, and vascular biology, (2001 Apr) 21 (4) 536-41.
 Journal code: 9505803. ISSN: 1524-4636.
 SO Arteriosclerosis, thrombosis, and vascular biology, (2001 Apr) 21 (4) 536-41.
 Journal code: 9505803. ISSN: 1524-4636.
 AB To define a role for the angiopoietin/Tie2 system in astrocytoma **angiogenesis**, we examined the expression of angiopoietin-1 (Ang1) and angiopoietin-2 (**Ang2**) in these tumors by immunohistochemistry and in situ hybridization. Furthermore, we studied in vitro the effects elicited by glioblastoma cell-secreted Ang1 or by recombinant Ang1 on functions of **endothelial** cells (ECs). Our observations of astrocytomas show that a stage-specific induction of angiopoietins occurs and is correlated with angiogenic phases. . . . vessels, Ang1 mRNA increased progressively in high-grade glioblastomas, in which the number of vessels was higher than in low-grade tumors. **Ang2** was detected in tumor cells and in ECs in high-grade astrocytomas, whereas its expression was negligible in low-grade tumors. Coculture of glioblastoma cell lines producing Ang1 with **endothelium** demonstrated a key role of this ligand in the control of EC network organization. We found that recombinant Ang1 in. . . results suggest that Ang1 directly acts on ECs by modulating cell-cell and cell-matrix associations and promoting the differentiation phase of **angiogenesis**.
 CT . . . Membrane Glycoproteins: ME, metabolism
 Membrane Glycoproteins: PD, pharmacology
 *Neovascularization, Pathologic: ME, metabolism
 Protein Biosynthesis
 Proteins: ME, metabolism
 Proteins: PD, pharmacology
Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors
 Research Support, Non-U.S. Gov't
 Tumor Cells, Cultured

L10 ANSWER 6 OF 10 MEDLINE on STN
 TI Biological action of angiopoietin-2 in a fibrin matrix model of angiogenesis is associated with activation of Tie2.
 AU Teichert-Kuliszewska K; Maisonpierre P C; Jones N; Campbell A I; Master Z; Bendeck M P; Alitalo K; Dumont D J; Yancopoulos G D; Stewart D J
 PY 2001
 SO Cardiovascular research, (2001 Feb 16) 49 (3) 659-70.
 Journal code: 0077427. ISSN: 0008-6363.
 SO Cardiovascular research, (2001 Feb 16) 49 (3) 659-70.
 Journal code: 0077427. ISSN: 0008-6363.
 AB The **endothelial** cell (EC) specific tyrosine kinase receptor, Tie2, interacts with at least two ligands, angiopoietin-1 (Ang1) and angiopoietin-2 (**Ang2**). Ang1 stimulates Tie2 receptor autophosphorylation, while **Ang2** has been reported to inhibit Ang1-induced Tie2 receptor autophosphorylation. We studied the effects of Ang1 and **Ang2** in an in vitro model of **angiogenesis**. Human ECs (HUVEC), cultured on 3-D fibrin matrices, were treated with conditioned media (CM) from stably transfected cells expressing human Ang1 or **Ang2**, or with purified recombinant proteins. EC tube formation was measured as a differentiation index (DI), calculated as the ratio of. . . and 19.13+/-7.86, respectively) vs. control (DI: 2.73+/-1.68 and 2.15+/-1.45, respectively, both P<0.001). Interestingly, CM from two independent cell lines overexpressing **Ang2** also produced a significant increase in EC differentiation (DI: 9.22+/-3.00 and 9.72+/-4.84, both P<0.005 vs. control) although the degree of **angiogenesis** was significantly less than that seen with Ang1. Addition of Ang1* (a genetically engineered variant of naturally occurring

Ang1) or **Ang2** also resulted in dose dependent increases in DI, which were blocked by an excess of soluble Tie2 receptor (20 microg/ml). Both Ang1* and **Ang2** induced modest increases in [3H]thymidine incorporation into HUVECs (20 and 26%, respectively), which were inhibited by excess soluble Tie2. Although **Ang2** was unable to induce significant Tie2 receptor phosphorylation during a 5-min exposure, a 24-h pretreatment with **Ang2**, followed by brief re-exposure, produced Tie2 phosphorylation in HUVEC comparable to that produced by Ang1*. These results demonstrate for the first time that **Ang2** may have a direct role in stimulating Tie2 receptor signaling and inducing in vitro **angiogenesis**. Our findings suggest that the physiological role of **Ang2** is more complex than previously recognized: acting alternately to promote or blunt Tie2 receptor signaling in **endothelial** cells, depending on local conditions.

CT

Analysis of Variance

Angiopoietin-1

Angiopoietin-2

Animals

Aorta

Blotting, Western

Cell Differentiation

Cell Division

Cell Line

Cells, Cultured

Dose-Response Relationship, Drug

***Endothelium, Vascular: ME, metabolism**

***Enzyme Inhibitors: PD, pharmacology**

Gels

Gene Transfer Techniques

Humans

Membrane Glycoproteins: GE, genetics

Membrane Glycoproteins: PD, pharmacology

Models, Biological

*Muscle, Smooth, Vascular: BS, blood supply

*Neoplasm Proteins: ME, metabolism

*Neovascularization, Physiologic

Proteins: GE, genetics

*Proteins: PD, pharmacology

*Proto-Oncogene Proteins

Rats

***Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors**

Receptor, TIE-2

Research Support, Non-U.S. Gov't

CN

0 (Agpt protein, rat); 0 (Angiopoietin-1); 0 (Angiopoietin-2); 0 (Enzyme Inhibitors); 0 (Gels); 0 (MEN1 protein, human); 0 (Membrane Glycoproteins); 0 (Neoplasm Proteins); 0 (Proteins); 0 (Proto-Oncogene Proteins); 0 (angiopoietin 1, . . .

L10

ANSWER 7 OF 10 MEDLINE on STN

TI

Angiotensin AT(1) and AT(2) receptors differentially regulate angiopoietin-2 and vascular **endothelial** growth factor expression and angiogenesis by modulating heparin binding-epidermal growth factor (EGF)-mediated EGF receptor transactivation.

AU

Fujiyama S; Matsubara H; Nozawa Y; Maruyama K; Mori Y; Tsutsumi Y; Masaki H; Uchiyama Y; Koyama Y; Nose A; Iba O; Tateishi E; Ogata N; Jyo N; Higashiyama S; Iwasaka T

PY

2001

SO

Circulation research, (2001 Jan 19) 88 (1) 22-9.
Journal code: 0047103. ISSN: 1524-4571.

TI

Angiotensin AT(1) and AT(2) receptors differentially regulate angiopoietin-2 and vascular **endothelial** growth factor expression and angiogenesis by modulating heparin binding-epidermal growth factor (EGF)-mediated EGF receptor transactivation.

SO

Circulation research, (2001 Jan 19) 88 (1) 22-9.
Journal code: 0047103. ISSN: 1524-4571.

AB

. . . growth factor (EGF)-like growth factor (HB-EGF) release followed by transactivation of EGF receptor (EGFR). Although Ang II and HB-EGF induce **angiogenesis**, their link to the angiopoietin (Ang)-Tie2

system remains undefined. We tested the effects of Ang II on Ang1, Ang2, or Tie2 expression in cardiac microvascular endothelial cells expressing the Ang II receptors AT(1) and AT(2). Ang II significantly induced Ang2 mRNA accumulations without affecting Ang1 or Tie2 expression, which was inhibited by protein kinase C inhibitors and by intracellular Ca(2+) chelating agents. Ang II transactivated EGFR via AT(1), and inhibition of EGFR abolished the induction of Ang2. Ang II caused processing of pro-HB-EGF in a metalloproteinase-dependent manner to stimulate maturation and release of HB-EGF. Neutralizing anti-HB-EGF antibody blocked EGFR phosphorylation by Ang II. Ang II also upregulated vascular endothelial growth factor (VEGF) expression in an HB-EGF/EGFR-dependent manner. AT(2) inhibited AT(1)-mediated Ang2 expression and phosphorylation of EGFR. In an in vivo corneal assay, AT(1) induced angiogenesis in an HB-EGF-dependent manner and enhanced the angiogenic activity of VEGF. Although neither Ang2 nor Ang1 alone induced angiogenesis, soluble Tie2-Fc that binds to angiopoietins attenuated AT(1)-mediated angiogenesis. These findings suggested that (1) Ang II induces Ang2 and VEGF expression without affecting Ang1 or Tie2 and (2) AT(1) stimulates processing of pro-HB-EGF by metalloproteinases, and the released HB-EGF transactivates EGFR to induce angiogenesis via the combined effect of Ang2 and VEGF, whereas AT(2) attenuates them by blocking EGFR phosphorylation. Thus, Ang II is involved in the VEGF-Ang-Tie2 system via. . .

CT . . .

Angiopoietin-1

Angiopoietin-2

Angiotensin II: PD, pharmacology

Animals

Calcium: ME, metabolism

Cells, Cultured

Cornea: BS, blood supply

Cornea: DE, drug effects

*Endothelial Growth Factors: GE, genetics

Endothelium, Vascular: CY, cytology

Endothelium, Vascular: DE, drug effects

Endothelium, Vascular: ME, metabolism

Enzyme Activation: DE, drug effects

*Epidermal Growth Factor: PH, physiology

Gene Expression Regulation: DE, drug effects

. genetics

Maleimides: PD, pharmacology

Membrane Glycoproteins: GE, genetics

Naphthalenes: PD, pharmacology

Neovascularization, Physiologic: DE, drug effects

*Neovascularization, Physiologic: PH, physiology

Protein Kinase C: AI, antagonists & inhibitors

Protein Kinase C: ME, metabolism

Protein-Tyrosine-Phosphatase: ME, metabolism

*Proteins: GE, genetics

Pyridines: PD, . . . genetics

RNA, Messenger: ME, metabolism

Rabbits

Rats

Receptor Protein-Tyrosine Kinases: GE, genetics

Receptor, Angiotensin, Type 1

Receptor, Angiotensin, Type 2

Receptor, Epidermal Growth Factor: AI, antagonists & inhibitors

*Receptor, Epidermal Growth Factor: GE, genetics

Receptor, Epidermal Growth Factor: ME, metabolism

Receptor, TIE-2

Receptors, Angiotensin: AI, antagonists & inhibitors

*Receptors, Angiotensin: PH, physiology

Receptors, Cell Surface

Receptors, TIE

Research Support, Non-U.S. Gov't

Tetrazoles: PD, pharmacology

Time Factors
Trans-Activation (Genetics)
Tyrphostins: PD, pharmacology
Vascular Endothelial Growth Factor A
Vascular Endothelial Growth Factors

CN 0 (Agpt protein, rat); 0 (Angiopoietin-1); 0 (Angiopoietin-2); 0 (Endothelial Growth Factors); 0 (Imidazoles); 0 (Indoles); 0 (Lymphokines); 0 (Maleimides); 0 (Membrane Glycoproteins); 0 (Naphthalenes); 0 (Proteins); 0 (Pyridines); 0. . . Type 1); 0 (Receptor, Angiotensin, Type 2); 0 (Receptors, Angiotensin); 0 (Receptors, Cell Surface); 0 (Tetrazoles); 0 (Tyrphostins); 0 (Vascular Endothelial Growth Factor A); 0 (Vascular Endothelial Growth Factors); EC 2.7.1.112 (Receptor Protein-Tyrosine Kinases); EC 2.7.1.112 (Receptor, Epidermal Growth Factor); EC 2.7.1.112 (Receptor, TIE-2); EC 2.7.1.112 (Receptors, . . .

L10 ANSWER 8 OF 10 MEDLINE on STN

TI Angiopoietin-2 at high concentration can enhance **endothelial** cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway.

AU Kim I; Kim J H; Moon S O; Kwak H J; Kim N G; Koh G Y

PY 2000

SO Oncogene, (2000 Sep 14) 19 (39) 4549-52.

Journal code: 8711562. ISSN: 0950-9232.

TI Angiopoietin-2 at high concentration can enhance **endothelial** cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway.

SO Oncogene, (2000 Sep 14) 19 (39) 4549-52.

Journal code: 8711562. ISSN: 0950-9232.

AB The angiopoietin-Tie2 system in **endothelial** cells is an important regulator of vasculogenesis and vascular integrity. High levels of angiopoietin-2 (**Ang2**) mRNA are observed in vascular activation during tumorigenesis. Although **Ang2** is known to be a naturally occurring antagonist of angiopoietin-1 (**Ang1**) in vivo, the exact function of **Ang2** itself is not known. Here, we found that a high concentration of **Ang2** (800 ng/ml) acts as an apoptosis survival factor for **endothelial** cells during serum deprivation apoptosis. The survival effect of high concentration **Ang2** was blocked by pre-treatment with soluble Tie2 receptor and the PI 3'-kinase-specific **inhibitors**, wortmannin and LY294002. Accordingly, 800 ng/ml of **Ang2** induced phosphorylation of Tie2, the p85 subunit of phosphatidylinositol 3'-kinase (PI 3'-kinase), and serine-threonine kinase Akt at Ser473 in the human umbilical vein **endothelial** cells; lower concentrations of **Ang2** (50 - 400 ng/ml) did not produce notable effects. These findings indicate that at high concentrations, **Ang2**, like **Ang1**, can be an apoptosis survival factor for **endothelial** cells through the activation of the Tie2 receptor, PI 3'-kinase and Akt, and thus may be a positive regulator of tumor **angiogenesis**. Oncogene (2000) 19, 4549 - 4552.

CT 1-Phosphatidylinositol 3-Kinase: AI, antagonists & inhibitors

1-Phosphatidylinositol 3-Kinase: DE, drug effects

*1-Phosphatidylinositol 3-Kinase: ME, metabolism

Androstadienes: PD, pharmacology

Angiopoietin-2

Apoptosis:. . . drug effects

Cell Line

Cell Survival: DE, drug effects

Chromones: PD, pharmacology

Culture Media, Serum-Free: PD, pharmacology

Dose-Response Relationship, Drug

*Endothelium, Vascular: CY, cytology

Endothelium, Vascular: DE, drug effects

*Endothelium, Vascular: ME, metabolism

Enzyme Inhibitors: PD, pharmacology

Humans

Morpholines: PD, pharmacology

Neoplasm Proteins: ME, metabolism

Neoplasm Proteins: PD, pharmacology
 Phosphorylation
 *Protein-Serine-Threonine Kinases
 *Proteins: . . .

CN 0 (Androstadienes); 0 (Angiopoietin-2); 0 (Chromones); 0 (Culture Media, Serum-Free); 0 (Enzyme **Inhibitors**); 0 (MEN1 protein, human); 0 (Morpholines); 0 (Neoplasm Proteins); 0 (Proteins); 0 (Proto-Oncogene Proteins); EC 2.7.1.112 (Receptor, TIE-2); EC 2.7.1.137. . .

L10 ANSWER 9 OF 10 MEDLINE on STN

TI Tumor necrosis factor-alpha upregulates angiopoietin-2 in human umbilical vein **endothelial** cells.

AU Kim I; Kim J H; Ryu Y S; Liu M; Koh G Y

PY 2000

SO Biochemical and biophysical research communications, (2000 Mar 16) 269 (2) 361-5.
 Journal code: 0372516. ISSN: 0006-291X.

TI Tumor necrosis factor-alpha upregulates angiopoietin-2 in human umbilical vein **endothelial** cells.

SO Biochemical and biophysical research communications, (2000 Mar 16) 269 (2) 361-5.
 Journal code: 0372516. ISSN: 0006-291X.

AB The angiopoietin-Tie2 system is an important regulator of vasculogenesis and vascular integrity. Angiopoietin-2 (**Ang2**) disrupts blood vessel formation in the developing embryo by antagonizing the effects of angiopoietin-1 (Ang1) on the Tie2 receptor. In this study, we examined the effect of a well-known proinflammatory cytokine, tumor necrosis factor-alpha (TNF-alpha), on **Ang2** expression in human umbilical vein **endothelial** cells. Reverse transcriptase-polymerase chain reaction and Northern blot analyses indicated that TNF-alpha induced **Ang2** mRNA expression in a time- and dose-dependent manner. Western blot analyses revealed that TNF-alpha treatment increased cellular **Ang2** protein. TNF-alpha induced less **Ang2** mRNA expression in the presence of nuclear factor-kappaB (NF-kappaB) **inhibitor**. These results suggest that TNF-alpha-induced inflammatory **angiogenesis** might be facilitated by the induction of **Ang2**.
 Copyright 2000 Academic Press.

CT Angiopoietin-2
 Base Sequence
 DNA Primers
 Endothelium, Vascular: CY, cytology
 *Endothelium, Vascular: DE, drug effects
 Endothelium, Vascular: ME, metabolism
 Humans
 NF-kappa B: AI, antagonists & inhibitors
 Neovascularization, Pathologic: GE, genetics
 *Proteins: GE, genetics
 RNA, Messenger: GE, genetics
 Recombinant Proteins: PD, . . .

L10 ANSWER 10 OF 10 MEDLINE on STN

TI Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis.

AU Maisonnier P C; Suri C; Jones P F; Bartunkova S; Wiegand S J; Radziejewski C; Compton D; McClain J; Aldrich T H; Papadopoulos N; Daly T J; Davis S; Sato T N; Yancopoulos G D

PY 1997

SO Science, (1997 Jul 4) 277 (5322) 55-60.
 Journal code: 0404511. ISSN: 0036-8075.

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 Journal code: 0404511. ISSN: 0036-8075.

AB **Angiogenesis** is thought to depend on a precise balance of positive and negative regulation. Angiopoietin-1 (Ang1) is an angiogenic factor that signals through the **endothelial** cell-specific Tie2 receptor tyrosine kinase. Like vascular **endothelial** growth factor, Ang1 is essential for normal vascular development in the mouse. An Ang1 relative, termed angiopoietin-2 (**Ang2**), was identified

by homology screening and shown to be a naturally occurring antagonist for Ang1 and Tie2. Transgenic overexpression of **Ang2** disrupts blood vessel formation in the mouse embryo. In adult mice and humans, **Ang2** is expressed only at sites of vascular remodeling. Natural antagonists for vertebrate receptor tyrosine kinases are atypical; thus, the discovery. . .

CT

Acid Sequence

Angiopoietin-1

Angiopoietin-2

Animals

Blood Vessels: EM, embryology

*Blood Vessels: ME, metabolism

Cells, Cultured

Cloning, Molecular

Embryo: ME, metabolism

Endothelial Growth Factors: GE, genetics

Endothelial Growth Factors: ME, metabolism

***Endothelium, Vascular: CY, cytology**

Endothelium, Vascular: ME, metabolism

Humans

Ligands

Lymphokines: GE, genetics

Lymphokines: ME, metabolism

Membrane Glycoproteins: AI, antagonists & inhibitors

Membrane Glycoproteins: ME, metabolism

Mice

Mice, Transgenic

Molecular Sequence Data

*Neovascularization, Physiologic

Phosphorylation

Proteins: CH, chemistry

*Proteins: ME, metabolism

Rats

Rats, Sprague-Dawley

***Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors**

Receptor Protein-Tyrosine Kinases: ME, metabolism

Receptor, TIE-2

Recombinant Fusion Proteins: ME, metabolism

Research Support, Non-U.S. Gov't

Signal Transduction

Vascular Endothelial Growth Factor A

Vascular Endothelial Growth Factors

CN 0 (Agpt protein, mouse); 0 (Agpt protein, rat); 0 (Angiopoietin-1); 0 (Angiopoietin-2); 0 (**Endothelial Growth Factors**); 0 (Ligands); 0 (Lymphokines); 0 (Membrane Glycoproteins); 0 (Proteins); 0 (Recombinant Fusion Proteins); 0 (Vascular **Endothelial Growth Factor A**); 0 (Vascular **Endothelial Growth Factors**); EC 2.7.1.112 (Receptor Protein-Tyrosine Kinases); EC 2.7.1.112 (Receptor, TIE-2)